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(54) METHOD FOR TREATING HUMAN DISEASES ASSOCIATED WITH AN INCREASED DEOXYRIBONUCLEIC ACID CONTENT IN EXTRACELLULAR SPACES OF TISSUES AND A MEDICINAL PREPARATION FOR CARRYING OUT SAID METHOD

(57) The invention relates to medicine. The inventive method for treating human diseases associated with an increased deoxyribonucleic acid content in extracellular spaces of tissues and organs, consists in orally injecting a DNA ferment in a quantity of 20 000-500 000 Kunz units in a day per 1 kg of the body mass. The single dose of the inventive medicinal preparation for treating human diseases associated with an increased deoxyribonucleic acid content in extracellular spaces of tissues and organs comprises 20 000-500 000 Kunz units of the DNAse ferment. The oral administration of the above-mentioned important doses of the preparation only allows the catalytically significant amount of DNAse to be absorbed into the systemic circulation in such a way that the dose-dependent treating effect thereof is exhibited.

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Description

Technical field

[0001] The invention relates to medicine and can be used for treating and prophylaxis of a wide range of human diseases associated with increased deoxyribonucleic acid content in extracellular spaces of tissues and organs.

[0002] The spectrum of such diseases is wide and includes:

- diseases of proliferative nature associated with speeded up reproduction and surplus death of own cells, for example - tumorous and hyperplastic processes; high level of extracellular DNA is associated with bad prognosis for such diseases (Lecomte T., at.al., Detection of free-circulating tumor-associated DNA in plasma of colorectal cancer patients and its association with prognosis. Int J. Cancer 2002 Aug. 10; 100(5):542-8);

- diseases of infectious nature associated with reproduction of infectious agent, such as bacterial, viral, fungous, protozoal infections, dysbacteriosis; in etiology of such diseases extracellular DNA is either an independent pathogenic factor (for example in case when infection is caused by DNA-containing viruses) or it contributes to microorganisms growth being a base of extracellular matrix of their colonies (Extracellular DNA required for bacterial biofilm formation, Cynthia B Whitchurch et al., Science. 2002 Feb. 22; 295(5559):1487),or taking part in microorganisms genetic transformation (Transformation of malaria parasites by the spontaneous uptake and expression of DNA from human erythrocytes. Deitsch K., Driskill C., Wellems T.: Nucleic Acids Res. 2001 Feb. 1;29(3):850-3), or it complicates the disease course by making a ground for purulent necrotic masses. (Zaman S.,et. al. Direct amplification of Entamoeba histolytica DNA from amoebic liver abscess pus using polymerase chain reaction, Parasitol Res. 2000 Sep; 86(9):724-8.); (With S.Sherry and L.R.Christensen. Presence and significance of desoxyribose nucleoprotein in the purulent pleural exudates of patients. Proc. Soc. Exp. Biol. Med., 1948, 68:179-84);

- diseases resulting from atrophic, degenerative and inflammatory changes in organs and tissues -for example systemic lupus erythematosus;here the extracellular DNA is one of the key factors of disease pathogenesis (Pisetsky D.S., Immune response to DNA in systemic lupus erythematosus. Isr Med Assoc J., 2001 Nov.; 3(11):850-3);

DNA originating from dying cells can speed up ageing process and tissues atrophy, US 6524578 B1.

Background art

[0003] Well - known are treatment methods of a range of listed diseases by enteral introduction of certain enzymes; the patent CA 2394856 A1 particularly describes enteral introduction of enzymes which destroy surface proteins, lipids and carbohydrates for treating infectious diseases. This method doesn't provide destruction of deoxyribonucleic acids as one of the basic components of both intercellular matrix of growing microorganisms and purulent detritus masses. That's why this method isn't effective enough for treating infectious diseases.

[0004] Well - known is a method of treating diseases associated with inflammation. The method consists in oral use of proteolytic and lipolytic enzymes Bromelain, GB 984464 A. The formulations used according to the described method also don't contain any enzymes which destroy deoxyribonucleic acids. Because of poor therapeutic effectiveness this method isn't used in clinical pharmacology as an independent method but as an auxiliary one (Bromelain: biochemistry, pharmacology and medical use, Maurer H.R., Cell Mol Life Sci 2001 Aug 58:pp.1234-45).

[0005] Well - known is a method of systemic enzyme therapy (SET) based on application of proteolytic enzymes compositions introduced in high doses orally or as enemas (Wrba, H. & Pecher, O. Enzymes: A Drug of the Future. Ecomed Verlagsgesellschaft AG & Co., 1993).

[0006] Well - known are also methods of treating human diseases associated with inflammation based on enteral introduction of enzyme complex which contains glycolytic, proteolytic and lipolytic enzymes as well as enzymes which destroy deoxyribonucleic acid (deoxyribonucleases, DNASes), GB 1005985 A.

[0007] The patent GB1005985 A describes a method of inflammatory diseases treatment consisting in oral introduction of enzymes combination, including streptodornase (streptococcal DNASE) and chemical anti-inflammatory substances; the patent indicates that use of proteolytic enzymes obtained from pancreas is preferable; the conclusion is also done that the dose of used enzymes doesn't influence the treatment efficacy.

[0008] Among the above known methods of treatment based on enteral use of DNASE enzymes the closest to the claimed one is a method of treatment of wide range of inflammation-associated diseases based on oral introduction of DNASE enzyme by taking Varidase tablets containing complex of streptokinase and streptodornase (DNASES). The treatment method is based on oral introduction of 4-8 Varidase tablets per day for treatment of some inflammation-associated diseases (ROTE LISTE Buch 2004; ISBN 3-87193-286-8, Rote Liste Service GmbH), and wass commonly

used: Continued marketing of a useless drug ('Varidase') in Panama. (Lee D., Lancet 1990 Mar, pp.335:667).

[0009] The main drawback of this method is low therapeutic and prophylactic efficacy of both treatment of gastrointestinal tract disorders and treatment of other organs diseases. The reason is lack of enzyme absorption into the system circulation. It is particularly mentioned in the article: Orally and rectally administered streptokinase. Investigation of its absorption and activity; (Oliven A., Gidron E.; Pharmacology, 1981 vol.22:pp.135-8).

[0010] Well-known is a medical preparation for oral administration (Varidase) containing streptococcal enzymes streptokinase (proteolytic enzyme) and streptodornase - streptococcal deoxyribonuclease. The preparation contains 10000 units of streptokinase and 2500 units of streptodornase in one tablet (ROTE LISTE Buch 2004; ISBN 3-87193-286-8, Rote Liste Service GmbH).

[0011] This preparation is selected as the prototype of the claimed medical preparation.

[0012] Low efficacy of the preparation became one of the main reasons that Varidase tablets were taken out of production, and their marketing authorizations were cancelled in many countries around the world, particularly, in USA. One of the arguments was their pharmacological inefficiency (Department of Health and Human Services Food and Drug Administration; Federal Register, Vol.50, N240; Dec.13, 1985).

Summary of the invention

[0013] The ground of this invention according to claims 1-7 is provided by creation of effective method for treating human diseases associated with increased deoxyribonucleic acid content in extracellular spaces of tissues and organs.

[0014] According to the invention (claims 1-7) this problem is solved in the following way: the method for treating human diseases associated with increased deoxyribonucleic acid content in extracellular spaces of tissues and organs, by enteral administration of DNASE enzyme wherein said enzyme is introduced in doses from 20 000 to 500 000 Kunz units per 1 kg of the body mass per day. According to the method DNASE enzyme can be introduced orally; according to the method dosage form can provide enzyme release in oral cavity; according to the method dosage form can provide enzyme release in stomach; according to the method dosage form can provide enzyme release in small intestine; according to the method dosage form can provide enzyme release in large intestine; according to the method DNASE enzyme can be introduced rectally.

[0015] The ground of this invention according to claims 8-13 is provided in the following way: the medical preparation for treating human diseases associated with an increased deoxyribonucleic acid content in extracellular spaces of tissues and organs contains bioactive substance - DNASE enzyme. The content of DNASE enzyme in the single dose of the preparation comprises 25 000 - 5 000 000 Kunz units; according to claim 8 said preparation can be realized in a form of tablet for oral administration; according to claim 8 said preparation can be realized in a form of capsule for oral administration; according to claim 8 said preparation can be realized in a form of rectal suppository; according to claim 8 said preparation can be realized in a form of chewing gum or oral-buccal pellicle, or sublingual tablet; according to claim 8 said preparation can be dosed as a toothpaste or gel toothpaste, or powder, or oral cavity rinse, chewing gum, oral buccal pellicle or sublingual tablet.

[0016] The applicant is not aware of any information sources, which could contain data on identical technical solutions. This fact allows making a conclusion that the said invention corresponds to the criterion "novelty" (N).

[0017] The applicant was first to discover that only high doses of the enterally given DNASE enzyme, exceeding 20000 KU/kg/day, can cause reliable increase of DNA - hydrolytic activity in urine, as well as increase of immunoreactive DNASE I enzyme in urine (Table 1). At doses range between 20 000 and 500 000 KU/kg/day such changes have dose-dependent character. Generally it is evidenced that enteral intake of DNASE in high doses results in absorption of catalytically significant quantities of the enzyme into the system circulation. Such discovery makes it possible to create effective oral dosage forms of DNASE for treating human diseases associated with increased deoxyribonucleic acid content in extracellular spaces of tissues and organs, outside the digestive system.

[0018] Thanks to invention's distinctive features a new important result is achieved: provided is efficacy and safety of treatment of a wide range of diseases associated with an increased deoxyribonucleic acid content in extracellular spaces of tissues and organs; besides that an important feature of the method is technical simplicity of application (both method and preparation).

[0019] The applicant hasn't discovered any information sources containing data about influence of said features on the technical result achieved thanks to them. On the applicants' opinion it testifies that present technical solution corresponds to the criteria "inventive step" (IS).

Brief description of the drawings

[0020] Hereinafter the invention is explained by detailed description of its application examples without any references on drawings.

Detailed description of the preferred embodiment

[0021] The calculated amount of bovine pancreatic DNASE I with activity 3500 KU/mg (made by Seravac; South African Republic) was diluted in water and introduced once per os to 24 healthy volunteers (3 volunteers per one dose). After that total urine was collected during 12 hours; DNA - hydrolytic activity of urine was determined using viscosimetric method; presence of bovine DNASE I in total DNASE I fraction was determined according to electrophoresis picture (gel electrophoresis with isoelectric focusing). Results are given in Table 1.

[0022] Application of the invention according to items 8-13 is illustrated by following examples:

Example 1

[0023] Solid dosage form of DNASE for oral administration consisting of:

Dry bovinel pancreatic DNAse	100 000 Kunz units
Magnesium stearate	2, 5 mg
Microcrystalline cellulose	50 mg
Lactose	To formation of a 200 mg tablet

[0024] The dosage form is prepared as follows: dry bovine pancreatic DNASE with activity 3500 KU/mg (made by Seravac; South African Republic) (on the basis of 100 000 Kunz units (about 28 mg per 1 tablet)) is mixed with Magnesium stearate, then moistened, granulated. Granulate is mixed with lactose and microcrystalline cellulose in the quantity necessary to obtain 200 mg tablets, and then the mixture is pressed into tablets.

Example 2

[0025] Capsular dosage form of DNASE for oral administration consisting of:

Dry bovine pancreatic DNASE	1 000 000 Kunz units
Magnesium stearate	2, 5 mg
Microcrystalline cellulose	40 mg

[0026] The dosage form is prepared as follows: dry bovine pancreatic DNASE with activity 3500 KU/mg (made by Seravac; South African Republic) (on the basis of 1 000 000 Kunz units (about 280 mg per 1 capsule)) is mixed with Magnesium stearate and Microcrystalline cellulose, then moistened, pressed and granulated. The granulated material is poured into cellulose capsules.

Example 3

[0027] Contents of fine dosage form for rectal use (1 suppository of 3 gram).

Bovine pancreatic DNASE	5 000 000 Kunz units
Solid fat base	1600 mg

Example 4

[0028] Dosage form of the preparation in form of plates for oral use (chewing gum).

Bovinel pancreatic DNAse	1 000 000 Kunz units
Gum base	2500 mg
Sugar, dextrose, tapioca, wax	to 3000 mg

[0029] Application of the said method is illustrated by following examples:

Example 5

[0030] Treatment of oncological diseases.

[0031] The research involved 9 patients taken into the surgery clinic with the diagnosis "breast cancer relapse". All the patients had gone through operative, chemical and radiation treatment of the disease before. By hospitalization all the patients had contraindications to surgery, chemical and radiation treatment. All the patients had measurable liver and/or lungs metastases. All the patients gave their consent on treatment carrying out. At the moment of treatment's start the expected life interval of the patients was not less than 3 months.

[0032] Group 1 (3 patients) was treated with placebo capsules during 3 months.

[0033] Group 2 (3 patients) was treated with capsules according to the Example 2. The daily dose was 5 000 000 Kunz units during 3 months.

[0034] Group 3 (3 patients) was treated with Varidase tablets (made by Wyeth) in maximum recommended dose which is 10 tablets in a day (25000IU of streptodornase in a day) during 3 months.

[0035] One of the patients from Group 3 was hospitalized in 9 weeks after treatment start because she suddenly felt worse, and metastasis was in progress. She died in the hospital on the third day after hospitalization.

[0036] In 3 months after treatment start the patients were readmitted to the hospital. All the patients had gone through computed tomography; clinical and biochemical blood study was performed. The general state of health was estimated according to Karnofsky scale.

[0037] All the patients from Groups 1 and 3 had enlarged metastatic nodes in liver and lungs; new metastatic centers appeared; Karnofsky index decreased by 30% on average. Three patients of five had noticeable worsening of blood values (decrease of albumin content in serum, intensification of hepatic cytolysis syndrome, anemia and biochemical signs of inflammation).

[0038] The repeated tomography of the patients from Group 2 didn't reveal any signs of old metastatic nodes' enlargement; appearance of new nodes was not noted as well.

[0039] In one case the Karnofsky index increased on 40%. Two other patients didn't have any changes of the Karnofsky index. All the three patients had increased content of serum albumin and blood hemoglobin.

Example 6

[0040] Treatment of infectious mononucleosis caused by EBV DNA- virus.

[0041] The research involved 20 patients from 15 to 28 years old with immunologically confirmed diagnosis - "infectious mononucleosis". The patients were divided into 3 groups:

Group 1 (8 patients) was treated with placebo tablets during 5 days and received standard symptomatic therapy (glucocorticoids and antibiotics).

Group 2 (6 patients) was treated with tablets according to the Example 1. The daily dose was 25 000 Kunz units per kg of the body mass during 5 days.

Group 3 (3 patients) was treated with Varidase tablets (made by Wyeth) in maximum recommended dose which is 10 tablets in a day (25000IU of streptodornase in a day) during 5 days.

Results of treatment see in Table 2.

Example 7

[0042] Treatment of maxilla-facial phlegmona.

[0043] The research involved 15 patients in medium heavy state of health, who were admitted to maxillofacial surgery hospital; the diagnosis was "maxillo-facial phlegmona".

The patients were divided into 3 groups:

[0044] Group 1 (5 patients) was treated with placebo tablets during three days and received standard antibacterial therapy during five days (cefotaxim 3g in a day intramuscularly).

[0045] Group 2 (5 patients) was treated with tablets according to the Example 1; the daily dose was 1 500 000 Kunz units (15 tablets) during 3 days. At the same time they received standard antibacterial therapy during 5 days (cefotaxim 3g in a day intramuscularly).

[0046] Group 3 (5 patients) was treated with Varidase tablets (made by Wyeth) in maximum recommended dose which

is 10 tablets in a day (25000IU of streptodornase in a day) during 3 days; at the same time they received standard antibacterial therapy during 5 days (cefotaxim 3g in a day intramuscularly).

[0047] Results of treatment see in table 3.

Example 8

[0048] Treatment of periodontitis.

[0049] The research involved 30 patients with medium heavy periodontitis. In the beginning of research dental deposit was removed from teeth of each patient; then they were instructed on cleaning according to the standard method - with use of tooth threads and interdental brushes. Patients were divided into 3 groups.

[0050] Group 1 - 10 patients used only Colgate toothpaste later on.

[0051] Group 2 - 10 patients used Colgate toothpaste later on as well as chewing gum with DNAse according to the Example 4 (1/4 plate was chewed during 30 minutes 4 times a day) during 4 weeks.

[0052] Group 3 - 10 patients used Colgate toothpaste later on as well as Varidase Buccal Tablets during 4 weeks.

[0053] Silness-Loe index (oral hygiene index) and Muellermann index (sulcus bleeding index) were evaluated before the beginning of research and by the end of it.

[0054] Results of research see in table 4.

Example 9

[0055] Treatment of SLE.

[0056] The research involved 16 patients with confirmed diagnosis "systemic lupus erythematosus" and symptoms of glomerulonephritis (proteinuria, microhematuria).

[0057] All the patients received a standard therapy (nonsteroid anti-inflamatory drugs, chloroquine). Patients from the experimental group (8 persons) were additionally treated with suppositories according to the Example 3; the dose was 250000 Kunz units per kg of the body mass in a day during 15 days. DNA concentration in plasma was studied before the start of treatment and by the end of treatment period. DNA content in plasma of control group patients had not reliably changed. Twice decrease of DNA in plasma was revealed in patients of the experimental group by the end of 15-days treatment course.

Example 10

[0058] Treatment of age-specific sperm motility impairment.

[0059] The research involved 18 healthy volunteers - men from 50 to 55 years old. The patients were divided into 3 groups:

Group 1 (7 patients) was treated with placebo-capsules during 30 days;

Group 2 (6 patients) was treated with capsules according to example 2; the daily dose was 35 000 Kunz units per kg of the body mass during 30 days;

Group 3 (5 patients) was treated with Varidase tablets (made by Wyeth) in maximum recommended dose which is 10 tablets in a day (25000IU of streptodornase in a day) during 5 days.

[0060] Sperm motility was studied in sperm samples taken from patients of three groups before the beginning of treatment and by the end of it. Before the beginning of treatment the percentage of mobile spermatozoids in sperm samples of patients from all three groups was 46%-54%. Patients from groups 1 and 3 didn't have any changes in motility of spermatozoids after treatment. Sperm samples of patients from the Group 2 contained 58%-62% of mobile spermatozoids after treatment.

Example 11

[0061] Influence of the treatment according claimed method on frequency of Rifampicin-resistant mutants.

[0062] Nasopharynx microflora was sowed in patient treated with Rifampicin (1), as well as in patient treated with Rifampicin simultaneously with treatment according to the said method (2). Seeding was performed on agar medium containing Rifampicin 50μg/ml. CFU number was estimated by means of serial dilutions with cloning on agar medium without antibiotic.

[0063] Results of research see in Table 5.

[0064] The table makes clear that the patient treated with antibiotic simultaneously with treatment according to the claimed method had much less bacterial load , and there were only a few Rifampicin-resistant bacterial clones among seeded microflora.

Example 12

[0065] Influence of the said method on the number of gentamycin-resistant mutants sowed patients.

[0066] Faeces' seeding was performed in patients who had taken gentamycin for treating acute intestinal infection. The seeding was performed the next day after the end of treatment. Hybrid cultures were grown in test-tubes as planctonic growth during 24 hours. The quantity of viable cells was estimated according to CFU (colony forming units) number after 24 hours-growing by subcloning to agar medium with antibiotic (Km, 50μg/ml). The table 6 shows average results for control patients group (Group A; 3 patients) and group of patients treated simultaneously according to the claimed method (Group B; 3 patients).

[0067] The table shows that the patients treated with antibiotic simultaneously with treatment according to the claimed method had much less load of gentamycin-resistant microorganisms.

Industrial applicability

[0068] Well-known materials are used for invention's implementation, what on applicant's opinion determines correspondence of the invention to the criterion "Industrial application" (IA)

Results of treatment efficacy research

[0069]

Table 1

Single dose of DNAse (KU\kg)	0	250	1000	10000	20000	35000	50000	100000	500000
DNA-hydrolytic activity in urine, KU\ml	0,11	0,13	0,09	0,085	0,9	5,2	10,3	17,0	37,9
Presence of bovine pancreatic D NAse I in the total fraction of blood DNAse	-	-	-	-	+	+	++	++	+++

Treatment results according to example 6

[0070]

Table 2

Syndrome	Terms of syndrome disappearance after disease manifestation (days)		
	group 1	group 2	group 3
Fever	12	7	11
Peripheral lymphadenopathia	16	9	17
Tonsillitis	15	11	14
Hepatosplenomegaly	17	12	18

Treatment results according to example 7

[0071]

Table 3

	Group 1	Group 2	Group 3
Terms of fever disappearance after treatment initiation	day 5	day 2	day 5
Terms of wound cleansing after treatment initiation	day 7	day 3	day 6
Wound closing after treatment initiation	day 12	day 7	day 11
Presence of microorganisms resistant to the antibiotic used	2 of 5	0	1 of 5

Research results according to example 8

[0072]

Table 4

Groups	Index	Before treatment	After treatment
group 1	Silness-Loe	1,77+\-0,27	1,31+\-0,35
	Muellerman	1,4+\-0,55	0,65+\-0,31
group 2	Silness-Loe	1,78+\-0,37	0,71+\-0,38
	Muellerman	1,35+\-0,67	0,29+\-0,21
group 3	Silness-Loe	1,74+\-0,35	1,23+\-0,45
	Muellerman	1,48+\-0,41	0,8+\-0,32

Research results according to example 11

[0073]

Table 5

Patient	CFU number	Number of Rifampicin-resistant clones
1	$(3,7+/-0,6)x10^9$	110
2	$(2,0+/-0,1)x10^8$	2-3

Research results according to example 12

[0074]

Table 6

	CFU number
Group A	$1,8x10^{10}$
Group B	$2,8x10^9$

Claims

1. Method for treating human diseases associated with increased deoxyribonucleic acid content in extracellular spaces of tissues and organs, by enteral administration of DNASE enzyme wherein said enzyme is introduced in doses from 20 000 to 500 000 Kunz units per 1 kg of the body mass per day.

2. Method according to claim 1 wherein DNASE enzyme is introduced orally.

3. Method according to claim 2 wherein dosage form provides enzyme release in oral cavity.

4. Method according to claim 2 wherein dosage form provides enzyme release in stomach.

5. Method according to claim 2 wherein dosage form provides enzyme release in small intestine.

6. Method according to claim 2 wherein dosage form provides enzyme release in large intestine.

7. Method according to claim 1 wherein DNASE enzyme is introduced rectally.

8. Medical preparation for treating human diseases associated with an increased deoxyribonucleic acid content in extracellular spaces of tissues and organs, containing bioactive substance - DNASE enzyme wherein the single dose of the said preparation comprises 25 000 - 5 000 000 Kunz units of enzymatic activity.

9. Medical preparation according to claim 8 wherein said preparation is realized in a form of tablet for oral administration.

10. Medical preparation according to claim 8 wherein said preparation is realized in a form of capsule for oral administration.

11. Medical preparation according to claim 8 wherein said preparation is realized in a form of rectal suppository.

12. Medical preparation according to claim 8 wherein said preparation is realized in a form of chewing gum or oral-buccal pellicle, or sublingual tablet.

13. Medical preparation according to claim 8 wherein said preparation is dosed as a toothpaste or gel toothpaste, or powder, or oral cavity rinse, chewing gum, oral buccal pellicle or sublingual tablet.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/RU 2006/000642

A. CLASSIFICATION OF SUBJECT MATTER

see supplemental sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 38/47, 9/02, 9/20, 9/48, 9/68, A61P 43/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PCT Online, USPTO DB, Esp@cenet, DWPI, CIPO (Canada PO), SIPO DB, AIPN, DEPATISnet, NCBI (PubMed), VINITIRU, SCSML.FSSI.RU

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2004/0157239 A1 (SEI-ICHI TANUMA et al.) 12.08.2004, the abstract, page 1 [0006]-[0008], page 7 [0100]-[0107], page 8 [0110], claims 25-29	1-13
A	RU 2207876 C1 (TKACHENKO VITALII VASILIEVICH) 10.07.2003, page 4, 5 column 1, page 6, column 1, page 8, page 14 column 1, page 17, column 1	1, 8
A	US 5484589 A (RUFELD, INC.) 16.01.1996, the abstract, column 1, 2	1, 2, 7-11
A	GB 1005985 A (ARMOUR PHARMACEUTICAL COMPANY) 29.09.1965, the claims, page 1, column 2	8

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
29 May 2007 (29.05.2007)	02 August 2007 (02.08.2007)
Name and mailing address of the ISA/ RU Facsimile No.	Authorized officer Telephone No.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/RU 2006/000642

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	VONMOOS PL. et al. Absorption and hematologic effect of streptokinase-streptodornase (varidase) after intracavital or oral administration.Schweiz Med Wochenschr, 1979 Oct 27;109(41): 1538-44, the abstract, on-line [Found in Internet] [found 29.05.2007] PMID:394315	1, 8

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

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REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

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- CA 2394856 A1 **[0003]**
- GB 984464 A **[0004]**
- GB 1005985 A **[0006] [0007]**

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